An Overview Of Systemic Candida Infections In Peri-operative Period And Intensive Care

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Abstract

OVERVIEW

As the anesthesiologists are about to involve with management of critically ill patients in intensive care settings as part of peri-operative medicine, the number of patients with systemic candidiasis in their practice will increase. Management of these patients has been a challenge to all intensive care specialists. Basic understanding of the pathophysiology and biology of these pathogens will increase the found of knowledge necessary to treat these patients and prevent the transmission of infectious agent to uninfected individuals.

INTRODUCTION

Fungal infections have dramatically increased in medical and surgical intensive care units with associated mortality and morbidity.([1]) ,([2]) Intensive care patients are by far susceptible to fungal infections during their stay in the hospital. Candida albicans has become a major nosocomial pathogen in the hospitals. It is the fourth leading cause for isolated positive blood cultures in U.S. hospitals.([3]) With increasing number of patients admitted to ICU, Candida infection will be a major challenge to the intensive care physician. The growing list of resistant pathogens, nosocomial transmission and lack of an effective antifungal drug with a lower toxicity, are the potential problems associated with systemic fungal diseases. Epidemiological studies have shown that Candida infections may be transmitted from patient to patient and from health care provider to patients.([4])

CANDIDA INFECTIONS

Fungi are eukaryotic organisms that reproduce both in sexual and asexual fusion. They have also been called molds, yeast and mushrooms. More than 80 species of Candida have been identified, but only eight are considered pathogenic: (i.e., C. albicans, C.stellatoidea, C. tropicalis, C. Keifyr, C. quilliermondi, C. krusei, C. parapsilosis, C. glabrata (torulopsis) and C. lusitaniae. Candidas are part of the normal flora of gastrointestinal tract, vagina and oral cavity of human.([5]) Phagocytosis by neutrophils and macrophages is the main host defense mechanism against tissue invasion and dissemination of fungi. Fungi have hydrolytic enzymes that damage membrane structure and results in tissue invasion. Major risk factors for Candida infections are listed in Table 1.

Table 1- Risk factors of Candidiasis

A. Immune suppression

- Chemotherapy
- Corticosteroid drugs
- Organ transplantation
- Neutropenia

B. Mechanical

- Burns
- Indwelling catheters
- Surgical Wounds
- Peritoneal dialysis
- Prosthetic implants (valves, joints, etc.)

C. Absence of normal flora

- Broad spectrum antibiotics

- Gastric acid-reducing treatment

D. Nutritional

- Hyperalimentation
- Obesity
- Chronic Acidosis
- Chronic malnutrition
- Alcohol and IV drug abuse

In addition to systemic involvement, Candida may result in superficial and locally invasive infections. The superficial infections are associated with alterations in hydration and acidity of skin, oropharynx, respiratory tract, gastrointestinal mucosa and other superficial tissues. Locally invasive forms of Candidiasis include esophagitis, pneumonitis, cystitis and pyelonephritis. Systemic Candidiasis whether in acute or chronic form refers to generalized dissemination of the pathogen. It involves major organs including heart, kidneys, liver, spleen, lungs, brain, peritoneum, joints and skeletal muscles. There is a period of systemic candidemia. Most of systemic infections are endogenous and originate from the gastrointestinal tract. However, indwelling catheters may serve as external sources of Candidiasis.

Eyes are often involved as a part of systemic dissemination, and therefore, ophthalmoscopic examination is an important diagnostic tool in detecting systemic Candida infections. Endophthalmitis manifests with orbital pain, blurred vision and scotoma, It results from retinal abscesses that gradually extend into vitreous humor. If untreated, it can lead complete blindness.

CANDIDA ENDOCARDITIS

The incidence of nosocomial endocarditis is rising. Candida infects native cardiac valves in IV drug users and patients receiving parentral nutrition. It may also occur following open heart surgeries. C. parapsilosis is the most common cause of endocarditis.($_{6}$) C.albicans and C. tropicalis can also cause fungal endocarditis, as well as pericarditis. Development of microabscesses invading the cardiac conduction system results in a complete heart block.($_{7}$) It is important to note that negative blood cultures do not rule out the possibility of Candida endocarditis.

URINARY TRACT INFECTIONS

C.albicans has been reported to cause 11% of all nosocomial urinary tract infection (UTI). ($_{8}$) Renal candidiasis is hematogenous and originate from gastrointestinal tract. Major risk factors for fungal UTI include the presence of foreign material in the urinary tract such as stents or stomal tubes, mechanical obstruction to the urine flow and renal transplantation. Candida can cause perinephric abscesses that may erode into the renal tubules, damage the renal cortex and cause tubular obstruction. The extension of fungi can turn into a fungus ball within the renal pelvis or ureters and lead to an obstruction and hydronephrosis. This may result in pyelonephritis with secondary fungemia and sepsis. Dissemination of fungi usually occurs with instrumentation of an immune suppressed or diabetic patient. Retrograde invasion of the kidneys may lead to papillary necrosis. Usual candiduria often resolves with changing the indwelling catheter.

CENTRAL NERVOUS SYSTEM (CNS) INFECTIONS

CNS involvement is generally seen following insertion of intra-ventricular shunting devices, however, it may also occur after skull fractures, chronic otitis media. Candida infection is associated with abscess formation, granulocytic vasculitis and meningitis. Direct staining of cerebrospinal fluid (CSF) reveals a positive result in less than 50% of the documented infections. Analysis of CSF usually demonstrates moderate increase in neutrophils and mononuclear cells. Intratecal administration of amphotericin B has been used with some success.($_{9}$)

RESPIRATORY SYSTEM

Candida is often a contaminant of respiratory tract and definite diagnosis can only be made by culturing the bronchial lavage fluid and/or bronchoscopic biopsy. Pulmonary involvement is usually blood borne.

GASTROINTESTINAL SYSTEM

Esophageal infection occurs primarily in patients with acquired immune deficiency (AIDS), post radiation and chemotherapy. Candida cholecystitis has a high mortality rate, and may extend into hepatosplenic infection in neutropenic patients secondary to aplastic anemia and acute leukemia.($_{10}$) Splenectomy has been recommended as a curative treatment for isolated splenic infections if there is no response to medical therapy.($_{11}$) Candida peritonitis has been reported in patients who have indwelling peritoneal catheter for dialysis (CAPD) or following an abdominal

surgery.([12]) Dissemination is frequent among children ([13]) . Antifungal treatment is the first line of treatment followed by removal of the catheter.

DIAGNOSIS

Candida is a part of normal flora and is often isolated from the urine, sputum and stool as a contaminant. The diagnosis of disseminated Candidiasis is often elusive since over 50% of blood cultures are negative. Serologic tests such as determination of complement-fixing antibody titer are useful in diagnosis of the candidiasis. Immune precipitation and latex agglutinin test are neither sensitive nor specific, therefore they are not considered a reliable tool of diagnosis of infection. Biochemical tests like determination of serum enolase has a similar results.

Pseudohyphae morphology on wet smear which is associated with positive culture results generally identifies superficial Candidiasis. Blood cultures have a low sensitivity but they have a very high specificity, therefore positive blood culture should be taken very seriously because of the rarity of false positive results. Staining with potassium hydroxide preparation and cultures can be done on biopsied tissue, as well as blood.

PROPHYLACTICS AND TREATMENT

Since there is no clear cut diagnostic criteria for systemic candidiasis, in the presence of persistent, unexplained fever in patients with some combination of neutropenia, prolonged ICU stay (>7 days), multiantibacterial therapy, indwelling central venous catheters, and colonization at one or more body sites with candida, empirical treatment is commonly suggested ([14]). Fungal prophylaxis has been successful in high risk patients. Use of nystatin in mucocutaneous candidiasis and local infections has been shown to decrease the incidence of systemic disease.([15]) In bone marrow transplant recipients, administration of fluconazole has decreased the incidence of Candida infections.([16]) In the presence of clinical signs of systemic candidiasis such as endophthalmitis and heavy colonization of the urine in high risk patients, empirical treatment may be indicated.

Amphotericin B, a polyene antibiotic, is the cornerstone of chemotherapy for disseminated fungal infections. Because of its very low solubility, this drug can only be administered via the intravenous route.([17]) Renal toxicity remains the most serious problem and decreases the therapeutic index of this agent.([18]) The recommended daily dose of amphotericin B is 0.4- 0.5 mg/kg, that can be doubled on alternate day for several weeks until the cumulative dose reaches a specified level which varies between 500 mg to 4 grams. Fever, chills, nausea, vomiting and rigors are also associated with amphotericin. Premedicating the patients with acetaminophen and diphenhydramine 30 min before amphotericin B usually controlls fever and chills. Rigors are generally treated with meperidine. Phlebitis is another complication associated with this agent which may be prevented with simultaneous infusion of heparin.

Nephrotoxicity is a major complication. Amphotericin B can cause renal vasoconstriction, renal tubular acidosis and increased urinary loss of potassium and magnesium. Serum electrolytes, blood urea nitrogen (BUN) and creatinine have to be followed, and the urine should routinely be monitored for cylindruria. If BUN rises greater than 50 mg/dl and/or serum creatinine increases more than 3.0 mg/dl, the drug should be temporarily discontinued or switched to a newer lipid-based generation if the candidemia persists ([19]). Preexisting prerenal azotemia increases the toxic effects of this agent. Prehydration with normal saline decreases the nephrotoxicity associated with amphotericin B. Potassium and magnesium replacement is usually required.

Because of the high toxicity of amphotericin B, new lipid-based delivery systems have been recently developed in order to diminish the systemic toxicity of the parent medication. Three common formulations in the market include ABLC (amphotericin B lipid complex), AmBiosome, and ABCD (amphotericin B cholloidal dispersion). They are available in three different shapes; sheet, disc and small unilamellar vesicles. These products contain between 10-50% mole amphotericin B and have half-life ranging between 26-150 minutes ([20],[21])

Oral fluconazole 400mg, can be used as an alternate to amphotericin B in immune competent patients. In the presence of immune deficiency, a combination therapy with fluconazole and flucytosine has been previously used ([22]). Combination therapy using amphotericin B and fluconazole is still contraversial.and is generally not recommended ([23],[24]). Advantages of fluconazole include a broad spectrum of activity, high therapeutic index and fewer side effects compared to amphotericin B ([25]). In high doses azole group of antifungal agents may produce liver dysfunction ranging from an asymptomatic rises of liver enzymes to overwhelming hepatic dysfunction ([26]). Common side effects include headache, nausea, vomiting and rarely alopecia and impotence. Emergence of resistant species such as C. krusie

has been reported with use of fluconazole ([27]). Furthermore, administration of oral medication may add an advantage of providing higher concentrations of antifungal medication to superficial candidiasis such esophagitis. Oral suspensions of itraconazole have been successfully used to treat candida esophagitis. The tissue concentration of this compound is several times higher than systemic levels because of a difference in tissue acidity.

Introccular injections of amphotericin B and S-flucytosine are used for treatment of candida endophthalmitis. If medical therapy fails, vitrectomy is recommended. Candiduria generally does not require a treatment unless it occurs in patients with kidney transplant and immune deficiency ([28]). Sources of candida should be identified and eliminated whenever possible. Treating the predisposing conditions such as low neutrophil count will increase the success rate of therapeutic intervention.

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